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Title:
2-(ARYLALKYLAMINO)PYRIMIDONE DERIVATIVES AND 2-(HETEROARYLALKYLAMINO)PYRIMIDONE DERIVATIVES

Abstract:

A pyrimidone derivative represented by formula (I) or a salt thereof, wherein R2 represents a hydrogen atom, a C1-2 perhalogenated alkyl group or a C1-6 alkyl group which may be substituted by 1 to 3 groups selected from a halogen atom, an amino, a (C1-6-alkyl)carbonylamino group, a (C1-6-alkoxy)carbonylamino group, a C1-6 alkylsulfonylamino group or a phenyl group; R3 represents a 2, 3 or 4-pyridyl group optionally substituted by a C1-4 alkyl group, C1-4 alkoxy group or a halogen atom; and when n represents 1 to 10, the R1 represents an unsubstituted naphth-1-yl group; an unsubstituted naphth-2-yl group; a C6,10 aryl group substituted by 1 to 3 substituents (A); a furan ring, thiophene ring, pyrrole ring or imidazole ring, the rings being optionally substituted by 1 to 3 substituents (A); an indole ring, attached by a carbon atom, optionally substituted by 1 to 3 substituents (A), the nitrogen of the indole ring being optionally substituted by a C1-6 alkyl group; a pyridine ring optionally substituted by 1 to 3 substituents (B); when n represents 4 to 10 then R1 can represent in addition an unsubstituted phenyl group; and when n represents 1 to 3 and R1 represents an unsubstituted phenyl group then R2 represents a C1-2 perhalogenated alkyl group or a C1-6 alkyl substituted by 1 to 3 groups selected from a halogen atom, an amino, a (C1-6-alkyl)carbonylamino group, a (C1-6-alkoxy)carbonylamino group and a C1-6 alkylsulfonylamino group. And a medicament comprising the said derivative or a salt thereof as an active ingredient which is used for preventive and/or therapeutic treatment of a neurodegenerative disease caused by abnormal activity of GSK3 beta .

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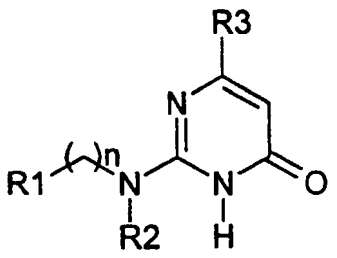

(I)

(57) Abstract: A pyrimidone derivative represented by formula (I) or a salt thereof, wherein R2 represents a hydrogen atom, a C_{1-2} perhalogenated alkyl group or a C_{1-6} alkyl group which may be substituted by 1 to 3 groups selected from a halogen atom, an amino, a (C_{1-6}-alkyl)carbonylamino group, a (C_{1-6}-alkoxy)carbonylamino group, a C_{1-6} alkylsulfonylamino group or a phenyl group; R3 represents a 2, 3 or 4-pyridyl group optionally substituted by a C_{1-4} alkyl group, C_{1-4} alkoxy group or a halogen atom; and when n represents 1 to 10, the R1 represents an unsubstituted naphth-1-yl group; an unsubstituted naphth-2-yl group; a $C_{6,10}$ aryl group substituted by 1 to 3 substituents (A); a furan ring, thiophene ring, pyrrole ring or imidazole ring, the rings being optionally substituted by 1 to 3 substituents (A); an indole ring, attached by a carbon atom, optionally substituted by 1 to 3 substituents (A), the nitrogen of the indole ring being optionally substituted by a C_{1-6} alkyl group; a pyridine ring optionally substituted by 1 to 3 substituents (B); when n represents 4 to 10 then R1 can represent in addition an unsubstituted phenyl group; and when n represents 1 to 3 and R1 represents an unsubstituted phenyl group then R2 represents a C_{1-2} perhalogenated alkyl group or a C_{1-6} alkyl substituted by 1 to 3 groups selected from a halogen atom, an amino, a (C_{1-6}-alkyl)carbonylamino group, a (C_{1-6}-alkoxy)carbonylamino group and a C_{1-6} alkylsulfonylamino group. And a medicament comprising the said derivative or a salt thereof as an active ingredient which is used for preventive and/or therapeutic treatment of a neurodegenerative disease caused by abnormal activity of GSK3β.

WO 01/70727 A1

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SPECIFICATION

2-(ARYLALKYLAMINO)PYRIMIDONE DERIVATIVES AND 2-(HETEROARYLALKYLAMINO)PYRIMIDONE DERIVATIVES

Technical Field

The present invention relates to compounds that are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of neurodegenerative diseases caused by abnormal activity of GSK3β.

Background Art

GSK3β (glycogen synthase kinase 3β) is a proline directed serine, threonine kinase that plays an important role in the control of metabolism, differentiation and survival. It was initially identified as an enzyme able to phosphorylate and hence inhibit glycogen synthase. It was later recognized that GSK3β was identical to tau protein kinase 1 (TPK1), an enzyme that phosphorylates tau protein in epitopes that are also found to be hyperphosphorylated in Alzheimer's disease and in several taupathies.

Interestingly, protein kinase B (AKT) phosphorylation of GSK3β results in a loss of its kinase activity, and it has been hypothesized that this inhibition may mediate some of the effects of neurotrophic factors. Moreover, phosphorylation by GSK3β of β-catenin, a protein involved in cell survival, results in its degradation by an ubiquitinilation dependent proteasome pathway.

Thus, it appears that inhibition of GSK3β activity may result in neurotrophic activity. Indeed there is evidence that lithium, an uncompetitive inhibitor of GSK3β, enhances neuritogenesis in some models and also increases neuronal survival, through the induction of survival factors such as Bcl-2 and the inhibition of the expression of proapoptotic factors such as P53 and Bax.

Recent studies have demonstrated that β-amyloid increases the GSK3β activity and tau protein phosphorylation. Moreover, this hyperphosphorylation as well as the neurotoxic effects of β-amyloid are blocked by lithium chloride and by a GSK3β antisense mRNA. These observations strongly suggest that GSK3β may be the link between the two major pathological processes in Alzheimer's disease : abnormal APP (Amyloid Precursor protein) processing and tau protein hyperphosphorylation.

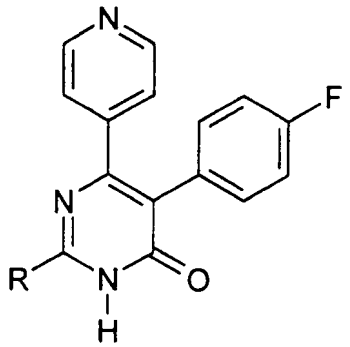
Although tau hyperphosphorylation results in a destabilization of the neuronal

cytoskeleton, the pathological consequences of abnormal GSK3β activity are, most likely, not only due to a pathological phosphorylation of tau protein because, as mentioned above, an excessive activity of this kinase may affect survival through the modulation of the expression of apoptotic and antiapoptotic factors. Moreover, it has been shown that β-amyloid-induced increase in GSK3β activity results in the phosphorylation and, hence the inhibition of pyruvate dehydrogenase, a pivotal enzyme in energy production and acetylcholine synthesis.

Altogether these experimental observations indicate that GSK3β may find application in the treatment of the neuropathological consequences and the cognitive and attention deficits associated with Alzheimer's disease, as well as other acute and chronic neurodegenerative diseases. These include, in a non-limiting manner, Parkinson's disease, tauopathies (e.g. frontotemporoparietal dementia, corticobasal degeneration, Pick's disease, progressive supranuclear palsy) and other dementia including vascular dementia; acute stroke and others traumatic injuries; cerebrovascular accidents (e.g. age related macular degeneration); brain and spinal cord trauma; peripheral neuropathies; retinopathies and glaucoma.

In addition GSK3β may find application in the treatment of other diseases such as: Non-insulin dependent diabetes (such as diabetes type II) and obesity; manic depressive illness; schizophrenia; alopecia; cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors.

PCT application WO 98/24782 discloses compounds represented by the following formula (A):



(A)

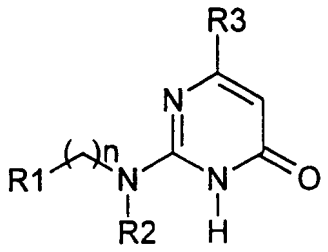
wherein R represents a 2,6-dichlorobenzyl group, a 2-(2-chlorophenyl)ethylamino group, a 3-phenylpropylamino group, or a 1-methyl-3-phenylpropylamino group. The compounds represented by formula (A) are characterized by a 4-fluorophenyl group at the 5-position of the pyrimidine ring. The main pharmacological activity disclosed for the compounds represented by formula (A) is an anti-inflammatory effect, whereas the compounds of the present invention represented by formula (I) herein below are useful as GSK3β inhibitors or as medicaments for the therapeutic treatment of neurodegenerative diseases, and therefore, their pharmacological activities are totally different.

Disclosure of the Invention

An object of the present invention is to provide compounds useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of neurodegenerative diseases. More specifically, the object is to provide novel compounds useful as an active ingredient of a medicament that enables prevention and/or treatment of the neurodegenerative diseases such as Alzheimer's disease.

Thus, the inventors of the present invention have identified compounds possessing inhibitory activity against GSK3β. As a result, they found that compounds represented by the following formula (I) had the desired activity and were useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of the aforementioned diseases.

The present invention thus provides pyrimidone derivatives represented by formula (I) or salts thereof, solvates thereof or hydrates thereof:



(I)

wherein:

R2 represents a hydrogen atom, a C_{1-2} perhalogenated alkyl group or a C_{1-6} alkyl group which may be substituted by 1 to 3 groups selected from a halogen atom, an amino, a (C_{1-6}-alkyl)carbonylamino group, a (C_{1-6} -alkoxy)carbonylamino group, a C_{1-6} alkylsulfonylamino group or a phenyl group;

R3 represents a 2, 3 or 4-pyridyl group optionally substituted by a C_{1-4} alkyl, group, C_{1-4} alkoxy group or a halogen atom; and

- When n represents 1 to 10, then R1 represents
  - an unsubstituted naphth-1-yl group;
  - an unsubstituted naphth-2-yl group;
  - a $C_{6,10}$ aryl group substituted by 1 to 3 substituents (A);

- a furan ring, thiophene ring, pyrrole ring or imidazole ring, the rings being optionally substituted by 1 to 3 substituents (A);
- an indole ring, attached by a carbon atom, optionally substituted by 1 to 3 substituents (A), the nitrogen of the indole ring being optionally substituted by a C_{1-6} alkyl group;

the substituent (A) being selected from a C_{1-6} alkyl group, halogen atom, a C_{1-2} perhalogenated alkyl group, a C_{1-3} halogenated alkyl group, a hydroxyl group, a C_{1-6} alkoxy group, methylenedioxy group, a nitro, a cyano, an amino, a C_{1-6} monoalkylamino group, a C_{2-12} dialkylamino group, a (C_{1-6}-alkyl)carbonylamino group, a ($C_{6,10}$-aryl)carbonylamino group, a (C_{1-6} -alkoxy)carbonylamino group, aminocarbonyl group, a (C_{1-6} monoalkylamino)carbonyl group, a (C_{2-12} dialkylamino)carbonyl group, a formyl, a C_{1-6} alkylcarbonyl group, a ($C_{6,10}$-aryl)carbonyl group, a C_{1-5} alkylsulfonyl group, a $C_{6,10}$ arylsulfonyl group, an aminosulfonyl group, a C_{1-6} monoalkylaminosulfonyl group, a C_{2-12} dialkylaminosulfonyl group, a phenyl group or a benzyloxy group;

the C_{1-6} alkyl groups and the C_{1-6} alkoxy groups being optionally substituted by a halogen atom, a hydroxyl group, a C_{1-6} alkoxy group, an amino, a C_{1-6} monoalkylamino group, a C_{2-12} dialkylamino group, a (C_{1-6} alkyl)carbonylamino group, a ($C_{6,10}$ aryl)carbonylamino group, a (C_{1-6} alkoxy)carbonylamino group, a C_{1-6} alkylsulfonylamino group, a $C_{6,10}$ arylsulfonylamino group, a phenyl group, a pyridine, a pyrimidine, or a pyrimidin-2-yl-amino;

- a pyridine ring optionally substituted by 1 to 3 substituents (B);

the substituent (B) being selected from a C_{1-18} alkyl group, a C_{3-8} cycloalkyl group, a C_{7-20} aralkyl group, a C_{6-10} aryl group, a fluorenyl group, a C_{1-6} alkoxy group, a C_{3-8} cycloalkyloxy group, a C_{7-20} aralkyloxy group, a C_{6-14} aryloxy group, a C_{1-5} alkylthio group, a C_{7-20} aralkylthio group, a C_{6-14} arylthio group, a C_{1-5} alkylsulfonyl group, a $C_{6,10}$ arylsulfonyl group, a halogen atom, a C_{1-2} perhalogenated alkyl group, a C_{1-5} halogenated alkyl group, a hydroxyl group, a cyano, a nitro, an oxo group, a formyl group, a C_{1-6} alkylcarbonyl group, a ($C_{6,10}$-aryl)carbonyl group, an amino, a C_{1-5} monoalkylamino group, a C_{2-10} dialkylamino group, or a heterocyclic ring having 1-4 hetero atoms selected from oxygen atom, sulfur atom, and nitrogen atom, and having total ring-constituting atoms of 5-10;

♦ When n represents 4 to 10 then R1 can represent in addition an unsubstituted

phenyl group; and

♦ When n represents 1 to 3 and R1 represents an unsubstituted phenyl group then R2 represents a C_{1-2} perhalogenated alkyl group or a C_{1-6} alkyl substituted by 1 to 3 groups selected from a halogen atom, an amino, a (C_{1-6}-alkyl)carbonylamino group, a (C_{1-6}-alkoxy)carbonylamino group and a C_{1-6} alkylsulfonylamino group.

According to another aspect of the present invention, there is provided a medicament comprising as an active ingredient a substance selected from the group consisting of the pyrimidone derivatives represented by formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof. As preferred embodiments of the medicament, there are provided the aforementioned medicament which is used for preventive and/or therapeutic treatment of diseases caused by abnormal GSK3β activity, and the aforementioned medicament which is used for preventive and/or therapeutic treatment of neurodegenerative diseases and in addition other diseases such as: Non-insulin dependent diabetes (such as diabetes type II) and obesity; manic depressive illness; schizophrenia; alopecia; cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors.

As further preferred embodiments of the present invention, there are provided the aforementioned medicament wherein the diseases are neurodegenerative diseases and are selected from the group consisting of Alzheimer's disease, Parkinson's disease, tauopathies (e.g. frontotemporoparietal dementia, corticobasal degeneration, Pick's disease, progressive supranuclear palsy) and other dementia including vascular dementia; acute stroke and others traumatic injuries; cerebrovascular accidents (e.g. age related macular degeneration); brain and spinal cord trauma; peripheral neuropathies; retinopathies and glaucoma, and the aforementioned medicament in the form of pharmaceutical composition containing the above substance as an active ingredient together with one or more pharmaceutical additives.

The present invention further provides an inhibitor of GSK3β activity comprising as an active ingredient a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the salts thereof, and the solvates thereof and the hydrates thereof.

According to further aspects of the present invention, there are provided a method for preventive and/or therapeutic treatment of neurodegenerative diseases caused by abnormal GSK3β activity, which comprises the step of administering to a patient a preventively and/or therapeutically effective amount of a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof; and a use of a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof for the manufacture of the aforementioned medicament.

As used herein, the C_{1-6} alkyl group represents a straight or branched alkyl group having 1 to 6 carbon atoms, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group, n-hexyl group, isohexyl group, and the like;

The C_{1-18} alkyl group represents a straight or branched alkyl group having 1 to 18 carbon atoms, for example in addition to the C_{1-6} alkyl group cited above, heptyl group, octyl group, nonyl group, decyl group, undecyl group, dodecyl group, tridecyl group, tetradecyl group, pentadecyl group, and octadecyl group;

The C_{3-8} cycloalkyl group represents for example a cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, and cyclooctyl group;

The $C_{6,10}$ aryl group represents a phenyl group, a naphth-1-yl group or a naphth-2-yl group;

The C_{7-20} aralkyl group represents for example a benzyl group, phenylethyl group, phenylpropyl group, phenylbutyl group, naphthylmethyl group, naphthylethyl group, naphthylpropyl group, and naphthylbutyl group;

The C_{1-6} alkoxy group represents an alkyl-oxy for example, methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, sec-butoxy group, tert-butoxy group, pentyloxy group, isopentyloxy group, neopentyloxy group, 1,1-dimethylpropyloxy group;

The C_{3-8} cycloalkoxy group represents a cycloalkyl-oxy for example, cyclopropoxy group, cyclobutoxy group, cyclopentyloxy group, cyclohexyloxy group, cycloheptyloxy group, and cyclooctyloxy group, and the like;

The C_{7-20} aralkyloxy group represents for example a benzyloxy group, phenylethyloxy group, phenylpropyloxy group, phenylbutyloxy group, naphthylmethyloxy group, naphthylethyloxy group, naphthypropyloxy group, and

naphthylbutyloxy group;

The C_{6-14} aryloxy group represents for example a phenoxy group, and naphthoxy group;

The C_{1-6} alkylthio group represents an alkyl-thio for example, methylthio group, ethylthio group, propylthio group, butylthio group and pentylthio group;

The C_{7-20} aralkylthio group represents for example a benzylthio group, phenylethylthio group, phenylpropylthio group, phenylbutylthio group, naphthylmethylthio group, naphthylethylthio group, naphthypropylthio group, and naphthylbutylthio group;

The C_{6-14} arylthio group represents for example a phenylthio group, and naphththio group;

The halogen atom represents a fluorine, chlorine, bromine or iodine atom;

The C_{1-2} perhalogenated alkyl group represents an alkyl group wherein all the hydrogen have been substituted by a halogeno, for example a CF_3 or C_2F_5,

The C_{1-3} halogenated alkyl or (or C_{1-5} halogenated alkyl group) represents an alkyl group wherein at least one hydrogen has not been substituted by a halogeno,

The C_{1-6} alkylcarbonyl group represents for example a acetyl group, propionyl group, butyryl group, and valeryl group;

The C_{1-6} monoalkylamino group represents an amino substituted by one C_{1-6} alkyl group, for example, methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group and isopentylamino group;

The C_{2-12} dialkylamino group represents an amino substituted by two C_{1-6} alkyl groups, for example, dimethylamino group, ethylmethylamino group, diethylamino group, methylpropylamino group and diisopropylamino group;

The (C_{1-6} alkyl)carbonylamino group represents an amino group substituted by a C_{1-6} acyl group, for example, formyl group, acetyl group, propionyl group, pivaloyl group, butyryl group, isobutyryl group, pentanoyl group, 3-methylbutyryl group, hexanoyl group;

The ($C_{6,10}$ aryl)carbonylamino group represents an amino group substituted by a benzoyl group or a naphthylenecarbonyl group;

The (C_{1-6} alkoxy)carbonylamino group represents an amino group substituted with a (C_{1-6} alkoxy)carbonyl group, such as for example, methoxycarbonyl group, ethoxycarbonyl group, propoxycarbonyl group, *tert*-butoxycarbonyl group, pentyloxycarbonyl group, hexyloxycarbonyl group;

The C_{1-6} monoalkylaminocarbonyl group represents an aminocarbonyl group substituted by one C_{1-6} alkyl group, as defined and illustrated above, for example :

methylaminocarbonyl group, ethylaminocarbonyl group, propylaminocarbonyl group, *i*-propylaminocarbonyl group, butylaminocarbonyl group, *iso*-butylaminocarbonyl group, *tert*-butylaminocarbonyl group, pentylaminocarbonyl group, neopentylaminocarbony group, 1,1-dimethylpropylaminocarbonyl group, n-hexylaminocarbonyl group, isohexylaminocarbonyl group, and the like;

The C_{2-12} dialkylaminocarbonyl group represents an aminocarbonyl group substituted by two C_{1-6} alkyl groups, as defined and illustrated above, for example : dimethylaminocarbonyl group, diethylaminocarbonyl group, dipropylaminocarbonyl group, di-*i*-propylaminocarbonyl group, butylaminocarbonyl group, *iso*-butylaminocarbonyl group, *tert*-butylaminocarbonyl group, dipentylaminocarbonyl group, di-neopentylaminocarbony group, di-(1,1-dimethylpropyl)aminocarbonyl group, di-n-hexylaminocarbonyl group, di-isohexylaminocarbonyl group, ethylmethylaminocarbonyl group, ethylpropylaminocarbonyl group, ethyl-*tert*-butylaminocarbonyl group, and the like;

The C_{1-6} alkylcarbonyl group represents an acyl group having 1 to 6 carbon atoms, such as, for example, formyl group, acetyl group, propionyl group, pivaloyl group, butyryl group, isobutyryl group, pentanoyl group, 3-methylbutyryl group, hexanoyl group;

The ($C_{6,10}$-aryl)carbonyl group represents an arylcarbonyl group wherein the $C_{6,10}$ aryl group is as defined here above, such as, for example benzoyl group and a naphthylenecarbonyl group;

The C_{1-5} alkylsulfonyl group represents an alkylsulfonyl group having 1 to 6 carbon atoms, such as, for example, methylsulfonyl group, ethylsulfonyl group, n-propylsulfonyl group, isopropylsulfonyl group, n-butyl group, isobutylsulfonyl group, sec-butylsulfonyl group, tert-butylsulfonyl group, n-pentylsulfonyl group, isopentylsulfonyl group, neopentylsulfonyl group, 1,1-dimethylpropylsulfonyl group;

The $C_{6,10}$ arylsulfonyl group represents an arylsulfonyl group wherein the $C_{6,10}$ aryl group is as defined here above, such as, for example, phenylsulfonyl group or naphthalenesulfonyl group;

The C_{1-6} alkylsulfonylamino or $C_{6,10}$ arylsulfonylamino represents respectively a sulfonylamino group substituted by a C_{1-6} alkyl or $C_{6,10}$ aryl group;

The C_{1-6} monoalkylaminosulfonyl group represents an aminosulfonyl group substituted by one C_{1-6} alkyl group, as defined and illustrated above, for example : methylaminosulfonyl group, ethylaminosulfonyll group, propylaminosulfonyl group, *i*-propylaminocarbonyl group, butylaminosulfonyl group, *iso*-butylaminosulfonyl group, *tert*-butylaminosulfonyl group, 1,1-dimethylpropylaminosulfonyl group, n-hexylaminosulfonyl group, isohexylaminosulfonyl group, and the like;

The C_{2-12} dialkylaminosulfonyl group represents a aminosulfonyl group substituted by two C_{1-6} alkyl group, as defined and illustrated above, for example : dimethylaminosulfonyl group, diethylaminosulfonyll group, dipropylaminosulfonyl group, *i*-propylaminocarbonyl group, butylaminosulfonyl group, *iso*-dibutylaminosulfonyl group, di-*tert*-butylaminosulfonyl group, di-(1,1-dimethylpropyl)aminosulfonyl group, di-n-hexylaminosulfonyl group, di-isohexylaminosulfonyl group, ethylmethylaminocarbonyl group, ethylpropylaminocarbonyl group, ethyl-*tert*-butylaminocarbonyl group, and the like.

The heterocyclic ring having 1-4 hetero atoms selected from oxygen atom, sulfur atom, and nitrogen atom, and having total ring-constituting atoms of 5-10 represents a furan ring, dihydrofuran ring, tetrahydrofuran ring, pyran ring, dihydropyran ring, tetrahydropyran ring, benzofuran ring, furopyridine ring, isobenzofuran ring, chromene ring, chroman ring, isochroman ring, thiophene ring, benzothiophene ring, thienopyridine ring, pyrrole ring, pyrroline ring, pyrrolidine ring, imidazole ring, imidazoline ring, imidazolidine ring, imidazopyridine ring, pyrazole ring, pyrazoline ring, pyrazolidine ring, triazole ring, tetrazole ring, pyridine ring, pyridine oxide ring, piperidine ring, pyrazine ring, piperazine ring, pyrimidine ring, pyridazine ring, indolizine ring, indole ring, indoline ring, isoindole ring, isoindoline ring, indazole ring, benzimidazole ring, purine ring, quinolizine ring, quinoline ring, isoquinoline ring, phthalazine ring, naphtyridine ring, quinoxaline ring, quinazoline ring, cinnoline ring, pteridine ring, oxazole ring, oxazolidine ring, isoxazole ring, isoxazolidine ring, thiazole ring, benzothiazole ring, thiazylidine ring, isothiazole ring, isothiazolidine ring, dioxane ring, dithian ring, morpholine ring, thiomorpholine ring, phthalimide ring and the like.

The compounds represented by the aforementioned formula (I) may form a salt. Examples of the salt include, when an acidic group exists, salts of alkali metals and alkaline earth metals such as lithium, sodium, potassium, magnesium, and calcium; salts of ammonia and amines such as methylamine, dimethylamine, trimethylamine, dicyclohexylamine, tris(hydroxymethyl)aminomethane, N,N-bis(hydroxyethyl)piperazine, 2-amino-2-methyl-1-propanol, ethanolamine, N-methylglucamine, and L-glucamine; or salts with basic amino acids such as lysine, δ-hydroxylysine, and arginine. The base-addition salts of acidic compounds are prepared by standard procedures well known in the art.

When a basic group exists, examples include salts with mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; salts with organic acids such as methanesulfonic acid, benzenesulfonic acid, p-

toluenesulfonic acid, acetic acid, propionic acid, tartaric acid, fumaric acid, maleic acid, malic acid, oxalic acid, succinic acid, citric acid, benzoic acid, mandelic acid, cinnamic acid, lactic acid, glycolic acid, glucuronic acid, ascorbic acid, nicotinic acid, and salicylic acid; or salts with acidic amino acids such as aspartic acid, and glutamic acid.

The acid-addition salts of the basic compounds are prepared by standard procedures well know in the art which include, but are not limited thereto, dissolving the free base in an aqueous alcohol solution containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and an acid in an organic solvent, in which case the salt separates directly, or is precipitated with a second organic solvent, or can be obtained by concentration of the solution. The acids which can be used to prepare the acid-addition salts include preferably those which produce, when combined with the free base, pharmaceutically-acceptable salts, that is, salts whose anions are relatively innocuous to the animal organism in pharmaceutical doses of the salts, so that the beneficial properties inherent in the free base are not compromised by side effects ascribable to the anions. Although medicinally acceptable salts of the basic compounds are preferred, all acid-addition salts are within the scope of the present invention.

In addition to the pyrimidone derivatives represented by the aforementioned formula (I) and salts thereof, their solvates and hydrates also fall within the scope of the present invention. The pyrimidone derivatives represented by the aforementioned formula (I) may have one or more asymmetric carbon atoms. As for the stereochemistry of such asymmetric carbon atoms, they may independently be in either (R) and (S) configuration, and the pyrimidone derivative may exist as stereoisomers such as optical isomers, or diastereoisomers. Any stereoisomers in pure form, any mixtures of stereoisomers, racemates and the like fall within the scope of the present invention.

Furthermore, as the pyrimidone derivatives represented by the aforementioned formula (I), a 3H-4-one compound, a 4-hydroxy compound, and a 1H-4-one compound may exist as tautomers. The existence of such tautomers is readily apparent to those skilled in the art, and these tautomers fall within the scope of the present invention.

Examples of preferred compounds of the present invention are shown in

table 1 thereafter. However, the scope of the present invention is not limited by these compounds.

Preferred compounds of the present invention represented by formula (I) include also compounds wherein R3 represents a 3- or 4-pyridyl group and more preferably 4-pyridyl group, which may be substituted by a C_{1-2} alkyl, group, C_{1-2} alkoxy group or a halogen atom.

More preferred compounds of the present invention represented by formula (I) include also

(1) Compounds wherein R3 represents a 4-pyridyl group which is unsubstituted.

(2) Compounds wherein n represents 1 to 5, and more preferably 1 to 4.

(3) When R1 is an indole ring, compounds wherein n is 2.

(4) When R1 is an indole ring, compounds wherein the indole ring is unsubstituted or (A) is selected from a C_{1-6} alkyl group, halogen atom, a C_{1-2} perhalogenated alkyl group, a C_{1-3} halogenated alkyl group, a hydroxyl group, a C_{1-6} alkoxy group, methylenedioxy group, a nitro, a cyano, an amino, a C_{1-6} monoalkylamino group, a C_{2-12} dialkylamino group, a (C_{1-6}-alkyl)carbonylamino group, a ($C_{6,10}$-aryl)carbonylamino group, a (C_{1-6} -alkoxy)carbonylamino group, aminocarbonyl group, a (C_{1-6} monoalkylamino)carbonyl group, a (C_{2-12} dialkylamino)carbonyl group, a formyl, a C_{1-6} alkylcarbonyl group, a ($C_{6,10}$-aryl)carbonyl group, a phenyl group, and a benzyloxy group, the alkyl or alkoxy group being unsubstituted; and preferably (A) is selected from a C_{1-6} alkyl group preferably a methyl, ethyl or propyl group; a halogen, a C_{1-4} alkoxy group and benzyloxy group.

(5) When R1 is an indole ring, compounds wherein R1 is a 3-indolyl ring.

(6) When R1 is a furan ring, thiophene ring, pyrrole ring or imidazole ring, compounds wherein R1 is unsubstituted or the substituent (A) is selected from a C_{1-6} alkyl group, halogen atom, a C_{1-2} perhalogenated alkyl group, a C_{1-3} halogenated alkyl group, a hydroxyl group, a C_{1-6} alkoxy group, methylenedioxy group, a nitro, a cyano, an amino, a C_{1-6} monoalkylamino group, a C_{2-12} dialkylamino group, a (C_{1-6}-alkyl)carbonylamino group, and a ($C_{6,10}$-aryl)carbonylamino group; and preferably compounds wherein R1 is unsubstituted.

(7) Compounds wherein R1 represents furan ring, thiophene ring or imidazole ring.

(8) When R1 is a pyridine ring, compounds wherein R2 is a hydrogen atom, a C_{1-5} alkyl group optionally substituted by a phenyl group, preferably R2 is a C_{1-3} alkyl group optionally substituted by a phenyl group and more preferably a

methyl, ethyl or n-propyl optionally substituted by a phenyl group.

(9) When R1 is a pyridine ring, compounds wherein (B) is being selected from a C_{1-6} alkyl group preferably methyl, ethyl or propyl group; a C_{1-6} alkoxy group preferably methoxy, ethoxy or propoxy group; a halogen atom or an amino.

(10) Compounds wherein R1 represents a substituted phenyl group.

(11) Compounds wherein R2 represents a hydrogen atom or a unsubstituted C_{1-3} alkyl group.

Particularly preferred compounds of the present invention represented by formula (I) include :

2-[[(3,4-dimethoxyphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[2-(4-methoxyphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[2-(3-methoxyphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[2-(2-methoxyphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[2-(2-fluorophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[2-(3-fluorophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[2-(4-fluorophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[2-(4-bromophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[2-(2,4-dichlorophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[2-(2-chlorophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[2-(4-chlorophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[2-(4-nitrophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[2-(4-aminophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[2-(2,5-dimethoxyphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[2-(4-hydroxyphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[2-(4-methylphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[2-(4-aminosulfonylphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[2-(3-chlorophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[4-(phenyl)butyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[2-(4-phenylphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[2-(2-naphthyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[[3-(aminomethyl)phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[[4-(aminomethyl)phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[(3-methylphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[(4-methoxyphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[(4-fluorophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,

2-[[(2-chlorophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[(4-chlorophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[[4-(trifluoromethyl)phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[[4-(3-aminopropoxy)phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[(3,4-dimethoxyphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[(3-nitrophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[(2-aminophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[(2-methylphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[(4-methylphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[(2-methoxyphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[(3-methoxyphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[(3-chlorophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[(4-aminophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[[3-(acetamidomethyl)phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[[3-(3-aminopropoxy)phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[[3-[(pyridin-2-yl)methoxy]phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[[3-[3-(pyridin-3-yl)propoxy]phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[[3-(*tert*-butyloxycarbonylaminomethyl)phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[(3-aminophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[[3-(benzoylaminomethyl)phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[[4-(2-aminoethoxy)phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[[3-(methanesulfonylaminomethyl)phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[[3-[(pyrimidin-2-yl)aminomethyl]phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[[3-(n-butylaminomethyl)phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[[3-(2-aminoethoxy)phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[[3-(4-aminobutoxy)phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[3-(2-methylphenyl)propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[3-(3-methylphenyl)propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[3-(4-methylphenyl)propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[3-(2-methoxyphenyl)propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[3-(3-methoxyphenyl)propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,

2-[[3-(4-methoxyphenyl)propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[3-(2-chlorophenyl)propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[3-(3-chlorophenyl)propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[3-(4-chlorophenyl)propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[[3-[3-(pyridin-4-yl)propoxy]phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[[3-[(pyridin-3-yl)methoxy]phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[[3-[2-(pyridin-2-yl)ethoxy]phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[[3-(*tert*-butyloxycarbonylaminomethyl)phenyl]methyl]methylamino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[[3-(methylamino)phenyl]methyl]methylamino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[3-(3,4-dimethoxyphenyl)]propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,
2-[[3-(4-phenylphenyl)]propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,

2-[[2-(1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,
2-[[2-(5-methoxy-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,
2-[[2-(5-methyl-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,
2-[[2-(5-benzyloxy-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,
2-[[2-(6-methoxy-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,
2-[[2-(6-fluoro-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,
2-[[2-(7-methyl-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,
2-[[2-[2-(1H-indol-3-yl)ethyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,
2-[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,
2-[[2-(1-methyl-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,

2-[(furan-3-yl-methyl)amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,
2-[[3-(1H-imidazol-1-yl)propyl]amino]-6-pyridin-4-ylpyrimidin-4(1H)-one, and
2-[2-(thiophen-2-yl-ethyl)amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,

6-(4-pyridyl)-2-(2-(2-pyridyl)ethylamino)-3*H*- pyrimidin-4-one,
6-(4-pyridyl)-2-(2-(3-pyridyl)ethylamino)-3*H*- pyrimidin-4-one,
6-(4-pyridyl)-2-(2-(4-pyridyl)ethylamino)-3*H*- pyrimidin-4-one,
6-(4-pyridyl)-2-(3-(2-pyridyl)ethylamino)-3*H*- pyrimidin-4-one,
6-(4-pyridyl)-2-(3-(3-pyridyl)ethylamino)-3*H*- pyrimidin-4-one and

6-pyridin-4-yl-[(pyrid-2-ylmehtyl)-amino]-3*H*- pyrimidin-4-one,
6-pyridin-4-yl-[(pyrid-3-ylmehtyl)-amino]-3*H*- pyrimidin-4-one,
6-pyridin-4-yl-[(pyrid-4-ylmehtyl)-amino]-3*H*- pyrimidin-4-one,
2-[methyl-(2-pyridin-2-yl-ehtyl)-amino]-6-pyridin-4-yl-3*H*-pyrimidin-4-one,

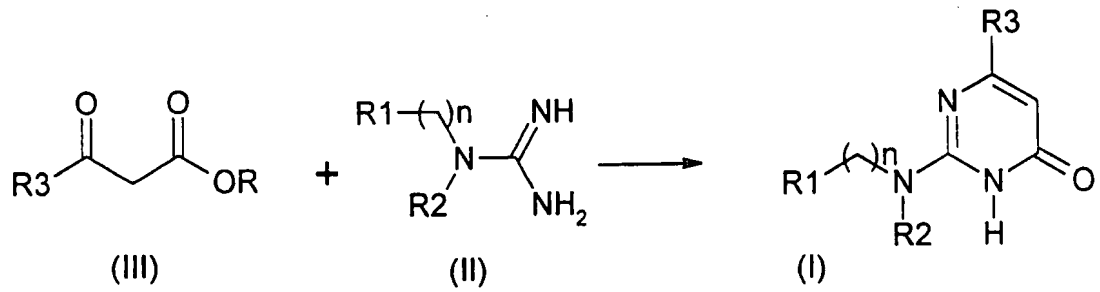
2-[benzyl-(2-pyridin-2-yl-ethyl)-amino]-6-pyridin-4-yl-3*H*-pyrimidin-4-one,
2-(phenethyl-pyridin-3-ylmethyl-amino)-6-pyridin-4-yl-3*H*-pyrimidin-4-one,
2-[phenethyl-(2-pyridin-2-yl-ethyl)-amino]-6-pyridin-4-yl-3*H*-pyrimidin-4-one,
n-{4-[(6-Oxo-4-pyridin-4-yl-1,6-dihydro-pyrimidin-2-yl)-phenethyl-amino]]-butyl}acetamide,
n-{4-[(6-Oxo-4-pyridin-4-yl-1,6-dihydro-pyrimidin-2-yl)-phenethyl-amino]-butyl}methanesulfonamide
2-{benzyl-[2-(2-methoxy-phenyl)-ethyl]-amino}-6-pyrydin-4-yl-3H-pyrimidin-4-one,
{4-[(6-Oxo-4-pyridin-4-yl-1,6-dihydro-pyrimidin-2-yl)-phenethyl-amino]-butyl}-carbamic acid *tert*-butyl ester,
2-[(4-amino-butyl)-phenethyl-amino]-6-pyridin-4-yl-3*H*-pyrimidin-4-one,
{4-[[2-(2-methoxy-phenyl)-ethyl]-(6-oxo-4-pyridin-4-yl-1,6-dihydro-pyrimidin-2-yl)-amino]-butyl}-carbamic acid *tert*-butyl ester,
2-{(4-amino-butyl)-[2-(2-methoxy-phenyl)-ethyl]-amino}-6-pyridin-4-yl-3*H*-pyrimidin-4-one,
2-[(4-hydroxy-butyl)-phenethyl-amino]-6-pyridin-4-yl-3*H*-pyrimidin-4-one,
2-[(4-amino-butyl)-(3-phenyl-propyl)-amino]-6-pyridin-4-yl-3*H*-pyrimidin-4-one,
2-(3-naphthalen-2-yl-propylamino)-6-pyridin-4-yl-3*H*-pyrimidin-4-one,
2-[2-(3-amino-propoxyl)-benzylamino]-6-pyridin-4-yl-3*H*-pyrimidin-4-one,
2-[2-(6-amino-hexyloxy)-benzylamino]-6-pyridin-4-yl-3*H*-pyrimidin-4-one,
6-pyridin-4-yl-2-[2-(3-pyridin-4-yl-propoxy)-benzylamino]-3*H*-pyrimidin-4-one and
2-[(3-phenyl-propyl)-trifluoromethyl-amino]-6-pyridin-4-yl-3*H*-pyrimidin-4-one.

As a further object, the present invention concerns also methods for preparing the pyrimidone compounds represented by the aforementioned formula (I).

These compounds can be prepared, for example, according to methods explained below.

1. Preparation Method 1

scheme 1



(III) (II) (I)

(In the above scheme, R represents an alkyl group, which may be substituted, and definitions of R1,R2, R3, and n are the same as those already described for compound of formula (I).)

The 3-ketoester represented by the above formula (III) is allowed to react with the compound represented by formula (II) or a salt thereof to obtain the compound of the aforementioned formula (I) in the presence of a base such as lithium tert-butoxide, sodium tert-butoxide, potassium tert-butoxide, lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, 1,8-diazabicyclo[5,4,0]undec-7-ene, triethylamine, diisopropyl-ethylamine, dimethylbenzylamine, dimethylaniline, diethylaniline and the like.

Examples of a solvent suitable for the reaction include, for example, alcoholic solvent such as methanol, ethanol, 1-propanol, isopropanol, tert-butanol; etheric solvents such as diethyl ether, tert-butyl methyl ether, tetrahydrofuran, isopropyl ether; hydrocarbon solvents such as benzene, toluene, xylene; halogenated solvents such as dichloromethane, chloroform, dichloroethane; aprotic polar solvents such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, dimethyl sulfoxide, sulfolane, hexamethylphosphoric triamide and the like. Generally, a single solvent or a mixture of two or more solvents may be used depending on the base used, and the reaction may be carried out for 1

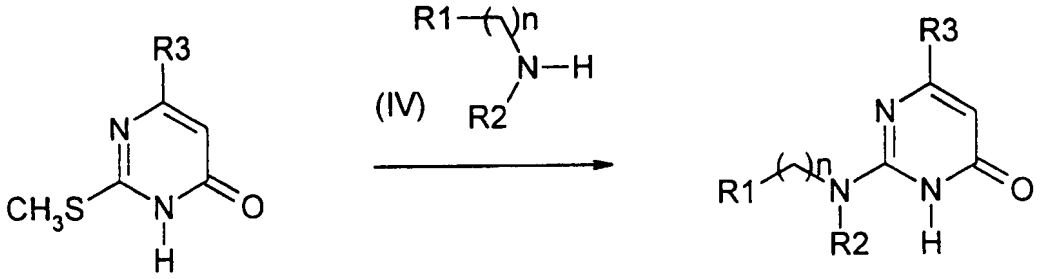
hour to 14 days at a suitable temperature ranging from 0° to 250°C under nitrogen or argon atmosphere or in ordinary air.

Compounds of formula (III) and formula (II) are commercially available or may be synthesized according to known methods of one skilled in the art.
For example compounds of formula (III), wherein R3 represent a 4-pyridyl group optionally substituted by a C_{1-4} alkyl group, C_{1-4} alkoxy group or a halogen atom, can be prepared by reacting a nicotinic acid optionally substituted by a C_{1-4} alkyl group, C_{1-4} alkoxy group or an halogen, with a malonic acid monoester. The reaction can be carried out using methods well known to one skilled in the art, such as for example in presence of a coupling agent such as 1,1'-carbonylbis-1H-imidazole in a solvent such as a tetrahydrofuran at a temperature ranging from 20 to 70°C.

2. Preparation method 2

Alternatively pyrimidone compounds represented by the aforementioned formula (I) may be prepared according to scheme 2.

Scheme 2



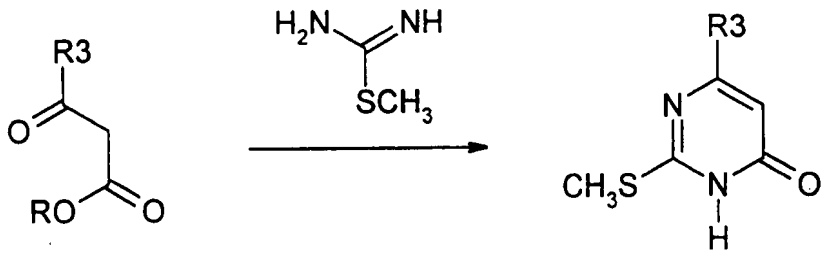
(In the above scheme the definition of R1, R2, R3 and n are the same as those already described.)

The 2-methylthio derivative represented by the above formula (V), wherein R3 is as defined for compound of formula (I), is allowed to react with an amine of formula (IV) to obtain the compound of the aforementioned formula (I). The reaction may be carried out in a solvent such as, for example, an alcoholic solvent such as n-pentanol or isoamyl alcohol at a suitable temperature ranging from 100

to 180 °C under ordinary air.

Compound of formula (V) may be prepared according to the method defined in scheme 3.

Scheme 3



(VI) (V)

(In the above scheme the definition of R3 is the same as already described.)

According to this method, the 3-ketoester of formula (VI) is allowed to react with a 2-methyl-2-thiopseudourea sulfate. The reaction may be carried out in solvent such as water or an alcohol, such as ethanol, propanol and butanol, at a suitable temperature ranging from 25-100°C under ordinary air.

Compounds of formula (IV) are commercially available or may be synthesized according to well-known methods of one skilled in the art.

In addition when applicable, compound of formula (I) could be derivatised into other compound of formula (I), using well known methods in the art. This is the case, for example, when R1 or a substituent on an alkyl or alkoxy group, could be oxidized, hydrogenated, alkylated..., or be transformed using well known method in the art to give another R1 group or a substituent within the scope of the present invention.

In the above reactions, protection or deprotection of a functional group may sometimes be necessary. A suitable protecting group can be chosen depending on the type of a functional group, and a method described in the literature may be applied. Examples of protecting groups, of protection and